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Jean-Marie Andrieu

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EXAMINER

LE, EMILY M

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1648

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.



## DETAILED ACTION

### *Status of Claims*

1. Claims 1-43, 45-51 are cancelled. Claims 44 and 52-56 are pending and under examination.

### *Claim Rejections - 35 USC § 103*

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Belardelli et al.<sup>1</sup>

In response to the rejection, Applicant argues that the Belardelli et al. does not teach the use of autologous virus. Applicant also argues that the Belardelli et al. would not motivate one of ordinary skill in the art to use autologous virus because the reference is focused on the process of preparing the dendritic cells and not the virus used to pulse the dendritic cells and that the animal models used by the reference makes it impossible for one of ordinary skill in the art to see any advantage in trying to replace the non-analogous virus with an autologous virus. Applicant additionally argues that Belardelli et al. teaches away from the use of autologous virus because the PBLs donors used by the reference are healthy donors and were screened for HIV-1 and hepatitis before donation. Applicant further argues that the teachings of Belardelli et al.

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<sup>1</sup> Belardelli et al. U.S. PreGrant Patent No. 2003/0092177 A1, filed April 27, 2001.

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cannot be extrapolated to a human system, and thus to an autologous virus because the composition of the reference induces a potent primary immune response and it induces production of antibodies, wherein the production of such antibodies are undesirable. To support this point, Applicant cited the teachings of Lu et al. Referring to Lu et al., Applicant notes that Lu et al. teaches that “[c]onsidering the humoral arm of the immune response after vaccination, it is interesting to observe that our inactivated whole HIV-1 loaded DC vaccine did not induce any neutralizing antibodies.” Lastly, Applicant argues that one of ordinary skill in the art would not have had a reasonable expectation of success for using autologous HIV virus because Lu et al. shows that IFN-gamma is a poor surrogate marker of the killing of HIV which contradicts the teachings of Belardelli et al., wherein Belardelli et al. teaches the that partially mature dendritic cells can only be obtained after a single step treatment that requires type 1 IFN as an essential factor and that Belardelli et al. refers to the mature cells as IFN-gamma producing cells.

Applicant's arguments have been considered, however, it is not found persuasive. The claims remain rejected for reason(s) of record. In the instant case, had Belardelli et al. teaches the use of autologous virus, the Office would have readily cited Belardelli et al. as anticipating the claimed rejection. However, the instant rejection is an obviousness rejection rather than an anticipation rejection.

Belardelli et al. teaches the use of dendritic cells as a cellular adjuvant in therapeutic compositions by pulsing the cells with inactivated HIV antigens. The only difference between the teachings of Belardelli et al. and the claimed invention, also as

noted in the rejection, is that Belardelli et al. did not pulse the autologous dendritic cells with inactivated autologous HIV. However, as noted in the rejection, due to the many variability in the many type of HIV isolates and the ability of the virus to mutate, it would have been prima facie obvious for one of ordinary skill in the art, at the time the invention was made, to use autologous HIV. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to induce an immune response against the specific HIV isolate infecting the subject.

The mere fact that Belardelli et al. is primarily focused on a process of preparing the cells, which acts as cellular adjuvant, is not a prima facie showing that the reference would not motivate one of ordinary skill in the art to pulse the cells with other inactivated viruses, including autologous HIV. In the instant case, Belardelli et al. clearly demonstrates that the cells are effective cellular adjuvants for antigens, including inactivated viruses. Similarly, the animal models used by Belardelli et al. is not a prima facie showing that the reference would not motivate one of ordinary skill in the art to pulse the cells with other inactivated viruses, including autologous HIV. The use of alternative antigens, including inactivated autologous HIV, is routinely practiced in the art. This is further evidenced by Belardelli et al., who uses different types of antigens, inactivated HIV and EBV peptides. One of ordinary skill in the art reading Belardelli et al. would not have limited his teachings to solely these two antigens, particularly since Belardelli et al. discloses that the cells can be used as an adjuvant to antigens, wherein by antigens, Belardelli et al. intends to encompass viral, bacterial and tumor antigens. [Paragraph 0041, in particular.]

Turning to Applicant's argument that Belardelli et al. teaches away from the claimed invention because the PBLs donors used by the reference are healthy donors and were screened for HIV-1 and hepatitis before donation, this is not found persuasive. The mere fact that Belardelli et al. uses healthy donors and screened the donors for HIV-1 and hepatitis is not a prima facie showing that the reference teaches away from the claimed invention. The reference in no way discredits or criticizes the use of inactivated autologous HIV. Had the reference discredits and/or criticizes the use of inactivated autologous HIV, and then the Office would agree with Applicant that the reference teaches away from the use of autologous HIV. However, this is not the case found in Belardelli et al.

Regarding Applicant's argument that the teachings of Belardelli et al. cannot be extrapolated to a human system because the composition of the reference induces a potent primary immune response and it induces production of antibodies, wherein the production of such antibodies are undesirable, and to support this position, Applicant cited Lu et al., it is not found persuasive. The Office has carefully reviewed the teachings of Lu et al. and Belardelli et al. Neither references support Applicant's assertion that production of antibodies are undesirable. While it is noted that Lu et al. teaches that "[c]onsidering the humoral arm of the immune response after vaccination, it is interesting to observe that our inactivated whole HIV-1 loaded DC vaccine did not induce any neutralizing antibodies", however, this statement does not support the assertion that production of antibodies is undesirable. Moreover, following the cited

teachings, Lu et al. clearly writes that the observation is "in keeping with the consensus that there is poor neutralizing antibody response during the course of HIV infection".

Regarding Applicant's last argument, that one of ordinary skill in the art would not have had a reasonable expectation of success for using autologous HIV virus because Lu et al. shows that IFN-gamma is a poor surrogate marker of the killing of HIV which contradicts the teachings of Belardelli et al., wherein Belardelli et al. teaches the that partially mature dendritic cells can only be obtained after a single step treatment that requires type I IFN as an essential factor and that Belardelli et al. refers to the mature cells as IFN-gamma producing cells; this has been considered, however, it is not found persuasive. It appears that Applicant has misconstrued the teachings of Belardelli et al. Belardelli et al. teaches the rapid generation of partially mature and highly functional dendritic cells with the use of single step treatment, that includes type I IFN, of freshly isolated monocytes. Belardelli et al. does not teach the use of IFN-gamma as a marker of the killing of HIV.

In summation, while all of Applicant's arguments have been considered, the rejection is maintained for reasons detailed herein and the record.

As presented in the 12/19/08 office action, the claims are directed to a composition comprising dendritic cells pulsed with an inactivated human immunodeficiency virus (HIV), wherein the dendritic cells are obtained from a monocyte by plastic-adherence followed by culture with GM-CSF and IL-4 and a pharmaceutically acceptable carrier, requires that the virus be autologous and wherein the virus is chemically inactivated by 2,2'-dithiopyridine. Additionally, the claims require that the

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virus be isolated from the blood tissue of the patient, and that composition be obtained by isolating peripheral blood mononuclear cells from whole blood, subjecting the peripheral blood mononuclear cells to plastic adherence, culturing the adherent cells with GM-CSF and IL-4 to obtain the dendritic cells, adding to 2,2'-dithiopyridine-inactivated virus to the dendritic cells and culturing the cells.

Belardelli et al. teaches composition comprising dendritic cells pulsed with an inactivated human immunodeficiency virus (HIV) and a pharmaceutically acceptable carrier. [Paragraphs 0066-0067 and 0071, in particular.] The dendritic cells used by Belardelli et al. were obtained from a monocyte by plastic-adherence followed by culture with GM-CSF and IL-4. Belardelli et al. uses AT-2, 2,2'-dithiopyridine, to chemically inactivate the virus. And Belardelli et al. uses autologous dendritic cells.

While the dendritic cells used by Belardelli et al. are autologous, it is not readily apparent if the virus used by Belardelli et al. is also autologous. It should be noted that Belardelli et al. uses the cells as an adjuvant, and the inactivated virus as an immunogen/antigen.

However, due to the many variability in the many type of HIV isolates and the ability of the virus to mutate, it would have been prima facie obvious for one of ordinary skill in the art, at the time the invention was made, to use autologous HIV. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to induce an immune response against the specific HIV isolate infecting the subject. One of ordinary skill in the art, at the time the invention was made, would have



had a reasonable expectation of success for doing so because the use of autologous antigens is routinely practiced in the art.

It is noted that the claims require the composition to expands *in vivo* expression of virus-specific CD8<sup>+</sup> T cells, and said virus-specific CD8<sup>+</sup> cells kill HIV-infected cells; however, MPEP § 2112 [R-3] (I) provides: [T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In *re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In *re Crish*, 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004), the court held that the claimed promoter sequence obtained by sequencing a prior art plasmid that was not previously sequenced was anticipated by the prior art plasmid which necessarily possessed the same DNA sequence as the claimed oligonucleotides. The court stated that "just as the discovery of properties of a known material does not make it novel, the identification and characterization of a prior art material also does not make it novel." *Id.*

In the instant case, while it may be true that Applicant discovers that the claimed composition expands *in vivo* expression of virus-specific CD8<sup>+</sup> T cells, and said virus-specific CD8<sup>+</sup> cells kill HIV-infected cells; however, this discovery does not make the composition patentable over the composition of Belardelli et al. Belardelli et al. teaches a composition that is the same as instantly claimed. The composition of Belardelli et al.

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is the claimed composition. Hence, Belardelli et al. does not need to teach that the composition expands *in vivo* expression of virus-specific CD8<sup>+</sup> T cells, and said virus-specific CD8<sup>+</sup> cells kill HIV-infected cells to anticipate the claimed invention. The composition of Belardelli et al. would have the same properties or functions recognized by Applicant.

Regarding the process by which the claimed product is made, it should be noted that even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” MPEP 2113, *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

In response to the previous rejection of the claims over Belardelli et al., Applicant argues that Belardelli et al. teaches away from the use of GM-CSF and IL-4 to obtain the dendritic cells. Applicant also argues that the reference does not teach the use of autologous HIV virus isolated from blood tissue of a patient. Applicant additionally asserts that the rejection is improper because it is not based on any fact on the record. Applicant submits the Gougeon declaration for consideration. Gougeon declaration asserts that in view of Richman<sup>2</sup>, one of ordinary skill in the art would have a reduced "expectation of successfully modifying Belardelli in the way the Official Action

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<sup>2</sup> Richman et al. Rapid evolution of the neutralizing antibody response to HIV type 1 infection. PNAS, April 2003, Vol. 100, No. 7, 4144-4149.

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proposes" because Richman noted difficulties associated with the experimental use of autologous HIV. The Gougeon declaration also states that the lack of reasonable expectation of successfully modifying Belardelli by using autologous HIV is underscored by the failure of others, Garcia et al.<sup>3</sup> Gougeon asserts that based on Garcia et al., who teaches that heat-inactivated vaccine was capable of eliciting "weak and transient" cellular immune responses and that based on such, it could be argued the vaccine did not elicit specific anti-HIV-1 immune response at all., one of ordinary skill in the art would not reasonable expect that the use of inactivated HIV to create a dendritic cell based vaccine would be successful in expanding the expression of CD8+ cells. Lastly, Applicant argues that the rejection improperly relies on an inherency type argument. Lastly, Applicant argues that the rejection improperly relies on an inherency type argument.

Applicant's arguments have been considered, however, it is not found persuasive. MPEP 2123 (II) provides, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). In the instant case, while Belardelli et al. does teach of several methods of generating production of dendritic cells, including one that is a preferred embodiment of Belardelli et al., however, it should be noted that Belardelli et al. does not teach away from the

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<sup>3</sup> Garcia et al. Therapeutic immunization with dendritic cells loaded with heat-inactivated autologous HIV-1 in patients with chronic HIV-1 infection. J. Infect. Dis. May 2005, Vol. 191, No. 10, 1680-1685.

use of GM-CSF and IL-4 for the reference does not criticize, discredit or otherwise discourage the use of such dendritic cells production method.

As recognized in the office action, the reference does not teach the use of autologous cells. Had the reference teaches such, the Office would have cited the reference in an anticipatory rejection instead of an obviousness rejection. To compensate for the noted deficiency in the prior art, the Office clearly and properly sets forth an obviousness rejection. Contrary to Applicant's assertion, an obviousness rejection need not to be limited to the teachings expressed therein, obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found **either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.** See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The Gougeon declaration, which has been considered, however, it is not sufficient to overcome the rejection. Regarding the assertion that "one of ordinary skill in the art would have a reduced "expectation of successfully modifying Belardelli in the way the Official Action proposes" in view of the teachings of Richman et al., Applicant is reminded that the standard is reasonable expectation of success and not absolute success. Additionally, it should be noted that the difficulties of Richman et al. is not directed at the making of autologous HIV. Rather the difficulties are directed at the measurement of neutralizing antibody responses. While it is noted that Richman et al. mentions that technical challenges are associated with the preparation of autologous

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virus that are typically obtained from peripheral blood mononuclear cells, however, as noted above, the standard is reasonable expectation of success. In the instant case, Richman et al. failed to demonstrate that one of ordinary skill would not be able to reasonable expect success in obtaining autologous HIV for use with the composition of Belardelli et al.

As for the Garcia et al. reference, which has been considered, however, it is not sufficient to demonstrate a lack of reasonable expectation of success. While Garcia et al. does note that that due to the weak and transient cellular immune response, it could be argued that the vaccine did not elicit specific anti-HIV-1 immune response at all, however, Garcia et al. does note that it could also be such conclusion could be argued against, which Garcia et al. details on page 1684. And, contrary to Applicant's assertion that one of ordinary skill in the art would not reasonably expect to elicit CD8+ T cell response, Garcia et al. was able to elicit HIV-1 specific CD8+ T cell response with the administration of a composition comprising autologous dendritic cells pulsed with inactivated whole autologous HIV-1 virus.

Regarding Applicant's assertion that the Office has improperly relied on an inherency type argument, which has been considered, however, it is not found persuasive. The rejection itself is not based on inherency. Rather inherency was used to evidence that the composition of Belardelli et al. also is capable of inducing CD8+ T cell response for it comprises the inactivated HIV virus as the antigen and dendritic cells to present the antigen to both helper and cytotoxic T cells required by the claimed invention. Belardelli et al. discloses that his composition induces CD8+ T cell.

4. Claims 52-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Belardelli et al., as applied above to claim 44, in view of Lu et al.<sup>4</sup>

In response to the rejection, Applicant submits the arguments presented above, and adds that Lu et al. fails to cure the deficiencies of Belardelli et al.

Applicant's argument has been considered, however, it is not found persuasive for reasons discussed in paragraph 3 of this office action. And, contrary to Applicant's assertion, while the composition of Belardelli et al. does not further comprise indinavir, Lu et al. teaches that indinavir direct up-regulate proliferation and down regulate apoptosis of T cells. [Paragraph bridging pages 247-248.] In the instant case, Lu et al., together with Belardelli et al. renders the rejected claims obvious.

As presented in the 12/19/08 office action, the claims require the composition to further comprise an adjuvant. The adjuvant is later limited to a protease inhibitor by claim 53, which depends on claim 52. The protease inhibitor is later limited indinavir by claim 54, which depends on claim 53. Claim 55, which depends on claim 54, later requires that the composition comprise a non-antiviral concentration of indinavir. And claim 56 limits the non-antiviral concentration to 10 nM.

The significance of Belardelli et al., as applied to claim 43, is provided above.

The composition of Belardelli et al. does not further comprise indinavir. However, Lu et al. teaches that indinavir direct up-regulate proliferation and down regulate apoptosis of T cells. [Paragraph bridging pages 247-248.]

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<sup>4</sup> Lu et al. HIV protease inhibitors restore impaired T-cell proliferative response in vivo and in vitro: a viral-suppression-independent mechanism. Blood, Jul 2000; Vol. 96, 250 - 258.

Thus, would have been prima facie obvious for one of ordinary skill in the art to combine the teachings of Belardelli et al. and Lu et al. One of ordinary skill in the art would have been motivated to do so to optimize CTL response against HIV infection. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because the determination of a workable or optimal range is routinely practiced in the art.

It is recognized that claims require the composition to contain non-antiviral concentration of indinavir, specifically 10 nM. In the instant, Lu et al. teaches that the extent in which indinavir up-regulate proliferation and down regulate apoptosis of T cells varies at different concentrations of indinavir. Thus, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to use any concentrations of indinavir, particularly since Lu et al. establishes that indinavir at various concentrations, ranging from .1nM to 1000 nM, stimulates direct up-regulate proliferation and down regulate apoptosis of T cells. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to determine the optimum concentration to optimize the proliferation of T cells. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because the determination of workable ranges or optimal value is routine practiced in the art.

### ***Conclusion***

5. No claim is allowed.

1. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to EMILY M. LE whose telephone number is (571)272-0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

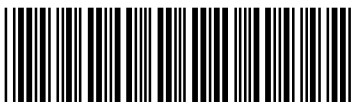


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/EMILY M LE/  
Primary Examiner, Art Unit 1648

/E. M. L./  
Primary Examiner, Art Unit 1648

**Search Notes (continued)**

Application/Control No.

10/600,361

Examiner

EMILY M. LE

Applicant(s)/Patent under  
Reexamination

ANDRIEU ET AL.

Art Unit

1648

**SEARCHED**

Class	Subclass	Date	Examiner

**INTERFERENCE SEARCHED**

Class	Subclass	Date	Examiner

**SEARCH NOTES  
(INCLUDING SEARCH STRATEGY)**

	DATE	EXMR
Updated previous search	10/12/2007	E.LE
USPAT, USPGPUB, DERWENT, EPO, JPO  Medline		
Keywords: IL-4 GM-CSF HIV Pulsed Dendritic		
Class/subclass searched in text.		
/E.Le/		
Updated previous search /E.L./	6/16/2008	E.LE
Updated previous search /E.L./	<b>12/15/2008</b>	<b>E.LE</b>
Updated previous search /E.L./	6/6/2009	E.LE